second paragraph, as indefinite; (4) 35 USC §102, as anticipated; and (5) 35 USC §103, as obvious over several references. These rejections are believed to be overcome in part by the above amendments and are otherwise traversed for reasons to be discussed below.

Overview of the Above Amendments

Claims 25-27 have been amended to make clear that the peptide claimed comprises a "PDGF A-chain homodimer comprised of two disulfide-linked chains." Support for these amendments can be found throughout the specification, including *inter alia* at page 2, lines 2-3 and page 12, lines 25-26. Thus, no new matter has been added to the application by the above amendments to the claims.

Rejection Under 35 USC §101

The Examiner rejected claims 25-27, 30-38 and 41, under 35 USC §101, as directed to nonstatutory subject matter. Specifically, the Examiner alleges that the phrase "substantially pure" does not serve to distinguish the instant product from nature. Applicants cannot agree.

As an initial matter, applicants submit that the correct statutory basis for such a "product of nature" rejection is 35 USC §102 and not 35 USC §101. Specifically, the provisions of §101 indicate that the classes of patentable subject matter include compositions of matter and processes. The instant claims clearly define compositions of matter and are therefore within the provisions of §101. The CCPA in In re Bergy, 195 USPQ 344 (CCPA 1977), in addressing product of nature rejections, stated:

> If it is not clear from the context that we were not discussing what is or is not statutory subject matter within Section 101 but only a difference between two cases which we found not to be a reason for distinguishing them, and that we were not expressing any view, even by way of dictum, on the patentability of living organisms

> as such, we now make it explicit that the thought underlying our presumption that Mancy could not have obtained a claim to the strain of microorganism he had described was simply that it lacked novelty. We were thinking of something preexisting and merely plucked from the Earth and claimed as such, a far cry from a biologically pure culture produced by great labor in a laboratory and so claimed. The dissenting board member was entirely correct in so interpreting our Mancy dictum. The examiner relied on it only to support his product-of-nature reasoning, and the board majority did not mention it, having abandoned that reasoning. Furthermore, it now appears to us, in light of what we have learned in this case about the separation and identification of new strains of Streptomyces, that our dictum was ill-considered. Had we known what we now know, we would likely have abjured the stated presumption.

Id. at 352.

Accordingly, §101 product of nature rejections are not in accord with the CCPA's views on the statute. Thus, applicants traverse the instant rejection as improper.

Even if such a rejection were properly taken under 35 USC §101, claims 30-38, the claims reciting protein which is "substantially pure", were copied from issued U.S. Patent No. 4,889,919. An examination of the prosecution history of this patent shows that the term "substantially pure" was added in order to distinguish the product claimed therein from nature. This amendment was considered adequate to overcome the 35 USC §101 rejection which had been stated against the original claims. Accordingly, since these claims were considered patentable and were allowed and issued, the instant claims, with the identical terminology, are similarly patentable and comply with the requirements of 35 USC §101.

Furthermore, it is well accepted that purification serves to distinguish a protein over that occurring in nature. This doctrine has been upheld in Scripps Clinic v. Genentech Inc., 3 USPQ 2d 1481 N.6 (N.D. Ca. 1987), wherein

the Court stated that a purified and concentrated preparation of Factor VIII:C constitutes a new combination not existing in nature, and hence was patentable under 35 USC §101.

Rejections Under 35 USC §112, First Paragraph

The Examiner rejected claims 39 and 40 under 35 USC §112, first paragraph, alleging that "the specification fails to adequately teach how to use the claimed pharmaceutical composition and the claimed invention lacks patentable utility." Furthermore, the Examiner is requiring that applicants demonstrate in vivo utility.

First of all, applicants believe they have indeed adequately taught how to use the claimed composition. The application, at pages 13-15, gives a detailed description of how one would prepare the PDGF compositions as well as apply the same for the treatment of wounds. Accordingly, applicants have provided guidelines in the specification which would aid one of skill in the art in selecting parameters for successful use of the pharmaceutical composition.

Furthermore, case law makes clear that the utility requirement is satisfied when an inventor has sufficient knowledge to justify the conclusion that a product is useful for a specific purpose. This, applicants have surely done. It is known that PDGF is stored in platelet α-granules and released locally during platelet activation when blood vessels are injured. It is also known that PDGF is a potent chemoattractant for monocytes and neutrophils and for fibroblast and smooth muscle cells. Accordingly, PDGF is instrumental in the tissue repair process. Thus, the basic biological activity of PDGF, including mitogenesis in responsive cells (such as fibroblasts), which is possessed by the proteins of the present invention, makes these proteins useful in enhancing the wound-healing process in

vertebrates. (See Example 5.3 in the specification.) Therefore, there is no reason to doubt the asserted utility for this peptide.

MPEP §608.01(p), in "Guidelines for Considering Disclosures of Utility in Drug Cases," expressly notes that the "Patent and Trademark Office shall confine its examination of disclosure of utility to the application of patent law principles, recognizing that other agencies of the government have been assigned the responsibility of assuring conformance to the standards established by statute for the advertisement, use, sale or distribution of drugs." Accordingly, "[I]f the asserted utility of a compound is believable on its face to persons skilled in the art in view of the contemporary knowledge in the art, then the burden is upon the Examiner to give adequate support for rejections for lack of utility." Indeed, in view of the explanation above, applicants submit that the asserted utility would have unquestionably been "believable on its face" to one skilled in the art.

With respect to the Examiner's requirement that applicants show that the PDGF composition demonstrates <u>in vivo</u> utility, applicants wish to point out that MPEP §608.01(p) requires clinical evidence only "if the utility relied on is directed <u>solely</u> to the treatment of humans" (emphasis in original). However, as is stated at page 13, lines 12-13, the instant invention is contemplated for use in other vertebrates, including domestic and farm animals, sports animals and pets. Furthermore, the Examiner in the '919 case stated in Paper No. 4 therein that <u>in vivo</u> utility was suggested by the art of record, which included the Johnsson et al. reference, also cited herein. Thus, the alleged utility of the PDGF composition is indeed adequate to satisfy the requirements of 35 USC §101.

Rejection Under 35 USC §101/35 USC §112, First Paragraph

The Examiner rejected claims 30-40, under 35 USC §101, or under 35 USC §112, first paragraph, as nonenabled. Specifically, the Examiner alleges that the "fragments claimed are not set forth in the specification, and therefore there is no description of how to make each fragment or how to use each fragment." Furthermore, the Examiner alleges that applicants have failed to show that all the fragments claimed would be biologically active. Again, applicants wish to remind the Examiner that these claims were copied from the '919 patent and were thus held to comply with the requirements of 35 USC §101 and §112 therein. Applicants wish to draw the Examiner's attention to the fact that the issued patent does not exemplify all the substitutions claimed.

Furthermore, one skilled in the art could easily make the claimed fragments using well-known techniques and test the same for activity using the mitogenic assay described in Example 5.3. The sequences, including the claimed fragments, are shown in Figures 1 and 2 of the instant application.

With regard to the Examiner's statement that "it cannot be expected that each fragment . . . would have mitogenic activity", the Examiner's attention is directed to the holding in Envirotech Corp. v. Al George, Inc., 221 USPQ 473, 480 (Fed. Cir. 1984) wherein an invention was held useful under 35 USC §101, the Court stating that "the fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." The Court went on to state that "the defense of non-utility cannot be sustained without proof of total incapacity." Similarly, the Court in Merck & Co. v. Danbury Pharmacal Inc., 8 USPQ 2d 1793, 1822 (D. Del. 1988) stated that "A claimed invention need not be unerringly

effective in its operations: all that is required is usefulness in some instances." The Court in E.I. du Pont de Nemours & Co. v. Berkeley & Co., Inc., 205 USPQ 1, similarly explained that only a small degree of utility is necessary and that partial success is sufficient to demonstrate patentable utility. Id. at n.17. "[L]ack of utility means the invention is 'incapable of achieving any of the aims of the patent under any conditions.'" Id. at n.10. Thus, applicants believe the claimed invention to comply with the requirements of 35 USC §101 and 35 USC §112, first paragraph.

Rejection Under 35 USC §112, First Paragraph

The Examiner rejected claims 25-27 under 35 USC §112, first paragraph, alleging that the term "substantially homologous" was overly broad. The Examiner acknowledges that the term is defined in the specification, however, argues that it is "highly unlikely that any amino acid within the PDGF A-chain protein could be substituted or deleted without some alteration of one or more of these functions." These claims, however, also include the limitation that the resulting PDGF be "functionally equivalent" to the PDGF shown in Figures 1 or 2. Page 6, lines 27-31 of the specification, explain that "functionally equivalent" intends that the sequence of the analog defines a chain that produces a protein having the biological activity of PDGF as measured by the assay described in Example 5. Accordingly, inoperative embodiments are excluded by this functional limitation (See, In re Dinh-Nguyen, 181 USPQ 46 (CCPA 1974), where it was held that implicit functionality can be relied on to exclude inoperable embodiments). Since applicants have taught how to make PDGF and since applicants have adequately taught how to assay for the activity of the same, it is submitted that

the present claims indeed comply with the requirements of 35 USC §112, first paragraph.

Rejection Under 35 USC §112, Second Paragraph

The Examiner rejected claims 25-27 and 30-41 under 35 USC §112, second paragraph. Specifically, it is alleged that the term "recombinant" is indefinite. However, the meaning of the term "recombinant" is certainly well known in the art. Furthermore, applicants do not understand the Examiner's comments regarding the patentability of the product claims versus the patentability of the process of obtaining the product in product-by-process claims. The Examiner has not stated in this §112 rejection, nor would it be proper for the Examiner to do so, an art rejection against the product claims. Thus, applicants believe the Examiner's comments are misplaced.

The Examiner rejected claims 30-41 as indefinite in their recitation of the term "substantially." To reiterate, these claims were copied from the '919 patent where there was no objection to the use of this term. Additionally, the term "substantially" has been held to be definite (Deering, Milliken & Co. v. Temp-Resisto Corp., 116 USPQ 386, 394 (S.D.N.Y. 1958). Thus, the claims are believed to comply with 35 USC §112, second paragraph.

Rejection Under 35 USC §102(a)

The Examiner rejected the claims under 35 USC §102(a) as being unpatentable over Betsholtz et al. Five of the six coinventors of the present invention are coauthors of the Betsholtz paper. This citation, in part, formed the basis of the instant disclosure. This is evidenced in a Rule 131 Declaration filed in the direct parent to the instant divisional application. A copy of this Rule 131 Declaration is submitted herewith for the Examiner's convenience. (See

paragraph 3 therein. Therefore, Betsholtz is not thought to be properly citable against the instant claims.

The Examiner rejected claims 25-27 as being anticipated by the '919 patent (to Murray). Specifically, the Examiner contends that Murray claims the "exact protein as applicants." Applicants do not dispute this fact. Indeed, claims 30-40 were copied based largely on claims 25-27, which were in the original application. However, 35 USC §102(e) is applicable to a patent granted on an application by another filed in the United States before the invention thereof by the applicant for patent. Accordingly, the provision is not appropriate where the applicant has invented prior to the patentee. Applicants submit that they invented the instantly claimed subject matter prior to Murray. Accordingly, Murray is not properly 102(e) citable art against the instant claims. Evidence that applicants were in possession of the invention prior to Murray can also be seen from the Rule 131 Declaration given in the parent case. Accordingly, this basis for rejection is improper.

The Examiner also rejected claims 25-27, 30-38 and 41 under 35 USC §102(b), as anticipated or, in the alternative, under 35 USC §103, as obvious over Heldin et al., Johnsson et al., or Antoniades et al. The Examiner contends that each of these references teaches the purification and characterization of PDGF but acknowledges that the references do not disclose the amino acid sequence of the PDGF A- or B-chains. Applicants cannot agree that these references either anticipate or render the instant claims obvious. Specifically, with respect to Heldin et al., this reference discusses osteosarcoma-derived growth factor (ODGF) and its relationship to PDGF. The authors speculate that ODGF might be composed of two A-chains related to PDGF A-chain. Sequence comparisons are only made with the 9 N-terminal amino acids. Although these sequences appear similar, there is no evidence that the remaining sequence

making up the A-chain of ODGF is the same as PDGF A-chain. Furthermore, there is no teaching regarding how to obtain PDGF A-chain homodimer, let alone produce it recombinantly. Indeed, the experimenters at page 513, second column, first paragraph, state:

> Fractionation of purified PDGF by various methods has not yielded any evidence for the presence of homodimers, and preliminary binding experiments indicate that PDGF from human platelets interacts with the PDGF receptor at higher affinity than ODGF (not shown). Taken together, these observations suggest that human PDGF may have a heterodimer structure consisting of both A- and B-chains which interacts with the PDGF receptor more avidly that the osteosarcoma-derived A-chain homodimer.

Accordingly, the citation actually teaches away from the concept of PDGF A-chain homodimers and emphasizes the differences between ODGF and PDGF. Applicants cannot, therefore, agree that the Heldin et al. reference either anticipates or renders the instant claims obvious.

With respect to Johnsson et al., this reference nowhere discloses a PDGF A-chain homodimer nor does it disclose the particular fragments recited in the instant claims. Additionally, the copied claims were specifically held patentable over this art, which was cited in the '919 case.

With regard to Antoniades et al., this reference also does not disclose how to obtain PDGF A-chain homodimer in a purified state, nor how to produce it recombinantly.

Finally, the Examiner rejected claims 39 and 40 under 35 USC §103 over the above references. Again, these claims are believed to be patentable for the reasons explained above.

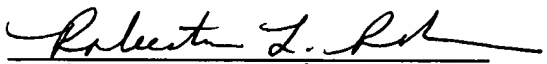
Conclusion

Applicants respectfully submit that the claims as amended comply with the requirements of 35 USC §101 and §112 and, furthermore, define an invention which is patentable

over the art. Accordingly, allowance is believed to be in order and an early notification to that effect would be appreciated.

If the Examiner notes any further matters which she believes would be expedited by a telephone interview, she is requested to contact the undersigned attorney at (415) 327-7250.

Respectfully submitted,

By: 
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